

# **EXHIBIT A104**



# Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)–Health Professional Version

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## Who Is at Risk?

Ovarian cancer is a rare disease, with carcinomas comprising approximately 90% of tumors and germ cell and stromal tumors accounting for the remainder. Ovarian carcinoma is a disease that predominantly affects postmenopausal women. Ovarian carcinomas consist of several histopathologic types, with high-grade serous being both the most common and most lethal. The category of ovarian borderline tumor or tumor of low-malignant potential, which historically had been considered in the context of ovarian cancer, is now generally considered a nonmalignant entity, although it has a postulated relationship with the development of some histologic subtypes of low-grade ovarian carcinomas.[1]

Risk factors for ovarian cancer include a family history of breast and/or ovarian cancer and inheritance of deleterious mutations in *BRCA1*, *BRCA2*, and selected other high-penetrance genes.[2-6] (Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information.) Other risk factors for ovarian cancer include obesity, tall height, endometriosis, and the use of postmenopausal hormone therapy.[7-9]

Associations of some risk factors with ovarian cancer vary by histopathologic subtype. The association of endometriosis with ovarian cancer is stronger for nonserous subtypes, especially clear cell carcinoma and endometrioid subtypes.[10] Further, among carriers of deleterious mutations in *BRCA1* or *BRCA2*, increasing evidence suggests that many tumors previously classified as ovarian high-grade serous carcinoma may develop from malignant cells arising in the tubal epithelium (serous tubal intraepithelial carcinoma [STIC]), although these tumors continue to be referred to as *ovarian* cancers in most writings. It is hypothesized that high-grade serous carcinomas among individuals who are not carriers of mutations in *BRCA1* or *BRCA2* may also develop in the fallopian tube, but few STICs have been identified among these women in the absence of concurrent high-stage disease. Further, data suggest that the distinction of high-grade serous carcinomas from other histologic types of high-grade carcinomas, particularly endometrioid carcinomas, is not reliable. Reported rates of mucinous carcinoma diagnoses have declined dramatically, but expert pathology reviews suggest that this reflects increased recognition of metastases from occult gastrointestinal primary tumors to the ovary, rather than a true decline in rates of ovarian primary tumors.[11]

Factors associated with a decreased risk of ovarian cancer include multiparity, use of oral contraceptives, multiple pregnancies, breastfeeding, tubal ligation, and salpingectomy.[12-15] Compared with nulliparous women, the risk of ovarian cancer is reduced by 30% to 60% among parous women, with additive protection for each additional birth.[16,17]

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## Overview

Note: Separate PDQ summaries on [Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Screening](#) and [Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment](#) are also available.

## Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

### Family history and inherited susceptibility to ovarian, fallopian tube, and primary peritoneal cancer

Based on solid evidence, women with a family history of ovarian cancer, especially in a first-degree relative, and those with an inherited predisposition to ovarian cancer, such as a *BRCA1* or *BRCA2* mutation, have an increased risk of developing ovarian cancer. (Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information.)

### Endometriosis

Based on fair evidence, self-reported and laparoscopically confirmed endometriosis is associated with an increased risk of ovarian cancer.[1,2] The association is stronger with nonserous histologic subtypes, specifically endometrioid and clear cell carcinomas.[2,3]

**Magnitude of Effect:** Modest with observed relative risks (RRs) of 1.8 to 2.4.

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Fair.

**External Validity:** Good.

### Hormone replacement therapy

Based on fair evidence, current or recent hormone therapy is associated with a small increased risk of ovarian cancer. Risks attenuate after hormone therapy is discontinued. Risks did not differ by preparation type (estrogen only vs. combined estrogen/progestin).[4,5]

**Magnitude of Effect:** Modest with observed RRs of 1.20 to 1.8.

**Study Design:** One randomized clinical trial, cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Fair.

**External Validity:** Good.

### Obesity and height

Based on fair evidence, increases in height and body mass index (BMI) are associated with a modest increased risk of ovarian cancer.

**Magnitude of Effect:** Based on an overview analysis of 25,157 women with ovarian cancer and 81,211 women without ovarian cancer from 47 epidemiological studies, the RR of ovarian cancer per 5 cm increase in height is

1.07 (95% confidence interval [CI], 1.05–1.09). The RR of ovarian cancer per 5 kg/m<sup>2</sup> increase in BMI is 1.10 (95% CI, 1.07–1.13) among never-users of hormone therapy and 0.95 (95% CI, 0.92–0.99) among ever-users of hormone therapy.[6]

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

### Oral contraceptives: benefits

Based on solid evidence, oral contraceptive use is associated with a decreased risk of developing ovarian cancer.

**Magnitude of Effect:** The degree of risk reduction varies by duration of oral contraceptive use and time since last use. For 1 to 4 years of oral contraceptive use, the RR reduction is 22%, and for 15 or more years of use, the RR reduction is 56%. The reduction in risk persisted for more than 30 years after use was discontinued, but the degree of reduction attenuated over time. The risk reduction per 5 years of oral contraceptive use was 29% for women who discontinued use less than 10 years ago and decreased to 15% for women who discontinued use 20 to 29 years ago. Ten years of use reduced cancer incidence before age 75 years from 1.2 to 0.8 per 100 users and reduced mortality from 0.7 to 0.5 per 100 users. The number needed-to-treat for 5 years was estimated to be about 185 women.

**Study Design:** Multiple case-control and cohort studies; meta-analyses.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### Oral contraceptives: harms

Based on solid evidence, combined current use of estrogen-progestin oral contraceptive use is associated with an increased risk of venous thromboembolism, particularly among smokers, for whom use is contraindicated. Oral contraceptives are not associated with a long-term increased risk of breast cancer but may be associated with a short-term increased risk while a woman is taking oral contraceptives. The risk of breast cancer declines with time since last use.

**Magnitude of Effect:** The risks may vary by preparation. Overall, the absolute risk of venous thromboembolism is about three events per 10,000 women per year while taking oral contraceptives. The risk is modified by smoking. Breast cancer risk among long-term (>10 years) current users is estimated at one extra case per year per 100,000 women. The risk dissipates with time since last use.

**Study Design:** Observational studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Tubal ligation: benefits**

Based on solid evidence, tubal ligation is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** Adjusting for other forms of contraception, tubal ligation provides a relative reduction in the odds of developing ovarian cancer of about 30%.

**Study Design:** Multiple case-control studies and cohort studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Tubal ligation: harms**

Based on fair evidence, harms include surgical risks, including the following:[7]

- Major morbidity including blood transfusion, reoperation, or hospital readmission (rate of 1.0 per 100 procedures).
- Minor morbidity including postoperative fever, urinary tract infections, or wound infections (rate of 6.0 per 100 procedures).

## **Multiparity**

Based on good evidence, multiparity is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** Based on good evidence from multiple observational epidemiological studies, parous women have an approximately 30% lower ovarian cancer risk than nulliparous women.[6,8,9]

**Study Design:** Observational epidemiologic studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Salpingectomy**

Based on limited data, salpingectomy is associated with a decrease in risk of ovarian cancer.

**Magnitude of Effect:** Approximately 50% decrease for bilateral salpingectomy, less protection for unilateral salpingectomy.

**Study Design:** Observational epidemiologic studies from several different countries.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Breastfeeding**

Based on solid evidence, breastfeeding is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** 2% decrease with every month of breastfeeding.[10]

**Study Design:** Multiple case-control and cohort studies; meta-analysis.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### **Risk-reducing bilateral salpingo-oophorectomy: benefits**

Based on solid evidence, risk-reducing bilateral salpingo-oophorectomy is associated with a decreased risk of ovarian cancer. Peritoneal carcinomatosis has been reported rarely following surgery. Risk-reducing surgery is generally reserved for women at high risk of developing ovarian cancer, such as women who have an inherited susceptibility to ovarian cancer.

**Magnitude of Effect:** 90% reduction in risk of ovarian cancer observed among women with a *BRCA1* or *BRCA2* mutation.

**Study Design:** Multiple case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### **Risk-reducing bilateral salpingo-oophorectomy: harms**

Based on solid evidence, prophylactic oophorectomy among women who are still menstruating at the time of surgery is associated with infertility, vasomotor symptoms, decreased sexual interest, vaginal dryness, urinary frequency, decreased bone-mineral density, and increased cardiovascular disease.

**Magnitude of Effect:** Reported prevalence of vasomotor symptoms varies from 41% to 61.4% among women who underwent oophorectomy before natural menopause. Women with bilateral oophorectomy who did not take hormone therapy were twice as likely to have moderate or severe hot flashes compared with women who underwent natural menopause. The RR of cardiovascular disease among women with bilateral oophorectomy and early menopause was 4.55 (95% CI, 2.56–9.01).

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Areas of Uncertainty**

### **Ovarian hyperstimulation for infertility treatment**

Evidence is poor to determine the association between ovarian hyperstimulation and the risk of ovarian cancer. Risk of ovarian cancer may be increased among women who remain nulligravid after being treated with ovarian



stimulating medications.

**Magnitude of Effect:** Uncertain—risk of invasive ovarian cancer may be increased among women who remain nulligravid after treatment; risk of borderline ovarian tumors may be increased among women treated with infertility drugs.

**Study Design:** Cohort and case-control studies; systematic review.

**Internal Validity:** Fair.

**Consistency:** Poor.

**External Validity:** Fair.

## References

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## Description of the Evidence

### Incidence and Mortality



In 2019, it is estimated that 22,530 new cases of ovarian cancer will be diagnosed and 13,980 deaths due to ovarian cancer will occur.[1] Incidence and mortality rates are higher among whites than among blacks, but statistically significant decreases in incidence and mortality rates have been observed among both whites and blacks.[2] In 2014, the overall incidence rate for ovarian carcinoma among women aged 65 years and older was 41.9 cases per 100,000 women-years.[3] Given that the Surveillance, Epidemiology, and End Results Program does not adjust for oophorectomy or salpingectomy, racial differences in the prevalence of women who had undergone these procedures could bias racial rate comparisons. A statistically significant decrease in delayed adjusted incidence of 0.9% among whites from 1987 to 2012 and 0.2% among blacks from 1992 to 2012 was observed. A statistically significant decrease in mortality rates of 2.0% per year among whites from 2002 to 2012 and 1.3% per year among blacks from 1992 to 2012 was observed. The population lifetime risk of ovarian cancer is 1.3%; the population lifetime risk of dying from ovarian cancer is 0.97%.[2]

## Histology and Pathogenesis of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Ovarian carcinoma is a biologically and clinically heterogeneous class of tumors that includes several major subtypes: serous, mucinous, endometrioid, and clear cell. Classification of ovarian carcinomas into type I and type II tumors has been proposed. In this system, type I tumors include the following:[4]

1. Endometriosis-related subtypes, such as endometrioid, clear cell, and seromucinous.
2. Low-grade serous.
3. Mucinous and malignant Brenner tumors.

Among type I tumors, endometrioid and clear cell carcinomas are numerically predominant and most important clinically. In general, type I ovarian carcinomas present at a lower stage than type II tumors and portend a better prognosis.

Type II tumors are comprised mainly of high-grade serous carcinomas, the most common and lethal of all ovarian carcinoma subtypes. These cancers usually present with symptomatic bulky stage III or IV disease and ascites. Many, but possibly not all, high-grade serous carcinomas appear to arise from malignant *in situ* lesions in the epithelium of the fallopian tube fimbria, which spread to the ovaries secondarily, but continue to be referred to as ovarian carcinomas. Evidence for a tubal origin is based mainly on examination of risk-reducing salpingo-oophorectomy specimens, performed among *BRCA1/BRCA2* mutation carriers, in which incidental low-volume disease enables recognition of serous tubal intraepithelial carcinoma (STIC). However, not all women with high-grade serous carcinomas have identifiable STIC and few studies of the fallopian tubes among women who are not carriers of *BRCA1/BRCA2* mutations have been performed, suggesting that pathogenesis of these tumors is not fully known. Serous carcinomas can be further divided on the basis of molecular characteristics.[5]

The heterogeneity in the etiology and pathogenesis of different ovarian cancer subtypes and variability in the classification of tumors over time and between studies pose challenges for interpretation of etiologic data. Ovarian cancer is a rare cancer, thus sample size and power of studies to detect moderate associations by cancer subtype is limited. However, clearer subtyping of cancers may assist in improving our understanding of the etiology of ovarian malignancies in future studies.

## Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

## Family history and inherited susceptibility to ovarian, fallopian tube, and primary peritoneal cancer

Some women are at an increased risk because of an inherited mutation, with the magnitude of that risk dependent on the affected gene and specific mutation. Underlying ovarian cancer risk can be assessed through accurate pedigrees and/or genetic markers of risk. Because of uncertainties about cancer risks associated with certain specific gene mutations, genetic information may be difficult to interpret outside of families with a high incidence of ovarian cancer.

This summary does not address multiple genetic syndromes or women who are at high risk because of inherited genetic factors. (Refer to the PDQ summaries on [Genetics of Breast and Gynecologic Cancers](#) and [Genetics of Colorectal Cancer](#) for specific information related to ovarian cancer risk associated with multiple genetic syndromes and ovarian cancer in *BRCA1/BRCA2* mutation carriers.)

## Hormone replacement therapy/hormone therapy

A meta-analysis of 52 studies (17 prospective and 35 retrospective) including 21,488 ovarian cancers found increased risks with current or recent hormone replacement use in prospective studies (relative risk [RR], 1.37; 95% confidence interval [CI], 1.29–1.46), with similar results for retrospective designs. Significant relationships were found for serous and endometrioid subtypes.[6] Recent use was strongly related to risk even among women who had used hormone replacement for less than 5 years (RR, 1.41; 95% CI, 1.32–1.50). Risk declined among women who had discontinued use, with greater effects for longer periods of cessation. Risks did not differ by preparation types (estrogen only vs. combined estrogen/progestin). Risks also did not differ by age at use.[7,8]

## Obesity and height

Ovarian cancer risk increases with increasing height and weight (body mass index [BMI]).[9] The Collaborative Group on Epidemiological Studies of Ovarian Cancer compiled individual data, both published and unpublished, from 47 epidemiological studies including 12,157 women with ovarian cancer and 81,311 controls. RR increased significantly with increasing height (1.07 per 5 cm height) and with increasing BMI (1.10 per 5 kg/m<sup>2</sup>). These findings were unaffected by other factors known to be associated with ovarian cancer risk, with the exception that ever-users of hormone therapy had no increased risk with increasing BMI. Given that height, weight, and BMI are thought to be strongly correlated, separating out the individual effects can be difficult. Ovarian cancer mortality has also been shown to be increased in obese women.[10,11]

## Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

### Oral contraceptives

A collaborative analysis was performed of individual data from 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 45 studies in 21 countries.[12] The studies included 13 prospective studies, 19 population-based case-control studies, and 12 hospital-based case-control studies. Oral contraceptive use was associated with a dose-response effect by duration of use, without observed changes in risk reduction by decade of use from the 1960s to 1980s, over which time the amount of estrogen in oral contraceptives was approximately halved. No risk reduction was observed for women who used oral contraceptives for less than 1 year. The risk reduction associated with use from 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 years or more was 0.78 (99% CI, 0.73–0.893), 0.64 (99% CI, 0.59–0.69), 0.56 (99% CI, 0.50–0.62), and 0.42 (99% CI, 0.36–0.49), respectively. The observed risk reduction persisted after cessation of oral contraceptive therapy but attenuated

over time since last use. The proportional reduction in risk per 5 years of use was 29% (95% CI, 23%–34%) for women who had discontinued use within the last 10 years; the reduction in risk was 15% (95% CI, 9%–21%) for women who discontinued use 20 to 29 years ago.

A meta-analysis, in which the primary analysis was restricted to 24 case-control and cohort studies published since 2000 to reflect more recent types of oral contraceptive preparations, also observed a dose-response by duration of use.[13] The risk reduction among women using oral contraceptives for more than 1 year but less than 5 years was 0.77 (95% CI, 0.66–0.89), and for women using oral contraceptives for more than 10 years, the risk reduction was 0.43 (95% CI, 0.37–0.51). The authors estimated that 185 women needed to be treated for 5 years to prevent one case of ovarian cancer. Based on an estimated lifetime risk of 1.38% and prevalence of ever-use of oral contraceptives of 83%, the authors estimated a lifetime reduction of ovarian cancer attributable to oral contraceptives of 0.54%.

(Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for specific information related to ovarian cancer risk among *BRCA1/BRCA2* mutation carriers.)

### Depot-medroxyprogesterone acetate

Limited information is available on the use of injectable progestational contraceptives (depot-medroxyprogesterone acetate [DMPA]) and the risk of ovarian cancer; studies are confounded by the use of other contraceptive methods, particularly oral contraceptives. A hospital-based study conducted in Mexico and Thailand, with 224 cases and 1,781 controls (the World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives), did not observe an association between DMPA and ovarian cancer (RR, 1.07; 95% CI, 0.6–1.8).[14] However, only 22 of the cases had ever used DMPA and nine of these had used it for 6 months or less.

A subsequent multicenter study conducted in 12 hospitals in Thailand, including 330 cases and 982 matched controls, observed a statistically significant decreased risk of ovarian cancer associated with DMPA use, controlling for oral contraceptive use and other associated factors (odds ratio [OR], 0.52; 95% CI, 0.33–0.88). A dose-response association was observed but the sample size was limited in longer-term use categories.[15]

### Tubal ligation

A meta-analysis of 16 case-control studies, three retrospective studies, and two prospective cohort studies observed a decreased risk of ovarian cancer associated with tubal ligation (RR, 0.66; 95% CI, 0.60–0.73).[16] The reduced risk was observed up to 14 years after tubal ligation. A population-based case-control study of 902 cases and 1,802 controls published subsequent to the meta-analysis observed an adjusted OR of 0.62 (95% CI, 0.51–0.75) associated with a history of a tubal ligation.[17] The association was adjusted for oral contraceptive use, which was also associated with a lower risk of ovarian cancer (OR, 0.62; 95% CI, 0.47–0.85) and other risk factors.[17]

Another pooling project with primary data from 13 population-based case-control studies examined the association between tubal ligation and ovarian cancer risk and included 7,942 epithelial ovarian cancers, and 13,904 controls.[18] Overall, tubal ligation was associated with a 29% reduction in risk (OR, 0.71; 95% CI, 0.66–0.77). The observed risk reduction varied by subtype of invasive cancers and was 52% (OR, 0.48; 95% CI, 0.40–49) for endometrioid cancer; 48% (OR, 0.52; 95% CI, 0.40–0.67) for clear cell cancer; 32% (OR, 0.68; 95% CI, 0.52–89) for mucinous cancer; and 19% (OR, 0.81; 95% CI, 0.74–0.89) for serous cancer.

A pooled analysis from 21 prospective cohort studies examined 14 hormonal, reproductive, and lifestyle factors by histologic subtype among 5,584 invasive ovarian cancers within a total sample of 1.3 million women. Overall,

tubal ligation was associated with an 18% reduction in risk (OR, 0.82; 95% CI, 0.73–0.93). The observed risk reduction varied by subtype of invasive cancer and was 40% (OR, 0.60; 95% CI, 0.41–0.88) for endometrioid cancer; 65% (OR, 0.35; 95% CI, 0.18–0.69) for clear cell cancer; and 9% (OR, 0.91; 95% CI, 0.79–1.06) for serous cancer. There was a nonsignificant increase in risk of 1% (OR, 1.01; 95% CI, 0.60–1.71) for mucinous cancer.[19]

## Breastfeeding

A meta-analysis [20] that included five prospective studies and 30 case-control studies examined the association between breastfeeding and the risk of ovarian cancer. Any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.76; 95% CI, 0.69–0.83). The risk of ovarian cancer decreased 8% for every 5-month increase in duration of breastfeeding (95% CI, 0.90–0.95). Another meta-analysis that included five prospective studies and 35 case-control studies found that any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.70; 95% CI, 0.64–0.76). These results are consistent with a previous meta-analysis and further support the prior finding of a suggested association between increased duration of breastfeeding and greater levels of protection.[21] Another meta-analysis of 19 studies, including four cohort and 15 case-control studies found an overall decreased risk of ovarian cancer with an OR of 0.66 (95% CI, 0.57–0.76) and an association with duration (2% decrease per month). The benefit of breastfeeding was greatest for the first 8 to 10 months.[22]

## Risk-reducing salpingo-oophorectomy

Risk-reducing surgery is an option considered by women who are at high risk of ovarian cancer, such as those with an inherited susceptibility to cancer. (Refer to the [Oral contraceptives](#) section in the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information on this as a risk-reducing intervention.) Among women in the general population, opportunistic salpingectomy, oophorectomy, or salpingo-oophorectomy have been considered as possible interventions at the time of surgery for other benign indications. Salpingectomy has also been discussed as a preferred means of sterilization.[23,24]

## Harms

Risks associated with benign oophorectomy (with or without salpingectomy or hysterectomy) have been analyzed in six published studies. Studies of three cohorts found that oophorectomy performed before menopause (age 45 or 50 years) was associated with increased overall mortality, likely related to cardiovascular disease. This finding was noted particularly among individuals not using hormone replacement. In the Women's Health Initiative, bilateral salpingo-oophorectomy was not associated with increased mortality. In the National Health and Nutrition Examination Survey (NHANES III), oophorectomy overall was not related to mortality, but mortality was increased among obese women younger than 40 years who did not use hormone replacement. The California Teachers Study did not find a mortality risk with oophorectomy, but only 3% of women did not use hormone replacement. Overall, data suggest that oophorectomy among younger women likely increases overall mortality and that this risk may be attenuated with hormone replacement.[25–30]

## Salpingectomy

Data relating salpingectomy to risk of ovarian/tubal cancer are limited, but consistent. A meta-analysis of three studies found an OR of 0.51 (95% CI, 0.35–0.71) for risk of these cancers among women who had undergone salpingectomy, compared with women who had intact fallopian tubes.[31] These studies included a Swedish record linkage study conducted from 1973 to 2009 with a mean follow-up of 23 years, which found the following hazard ratios (HRs) for risk of ovarian cancer compared with women who had not undergone surgery:

- For hysterectomy, the HR was 0.79 (95% CI, 0.70–0.88).
- For hysterectomy with bilateral salpingo-oophorectomy, the HR was 0.06 (95% CI, 0.03–0.12).

- For salpingectomy, the HR was 0.65 (95% CI, 0.52–0.81).
- For sterilization procedures, the HR was 0.72 (95% CI, 0.64–0.81).

Protection for bilateral salpingectomy was approximately twice that for unilateral salpingectomy.[32] This report included limited covariate data but results were similar to other smaller studies included in the meta-analysis.

Limited data based on circulating surrogate markers of ovarian reserve suggest that salpingectomy does not have an adverse effect on ovarian function.[33,34]

## **Factors With Inadequate Evidence of an Association Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer**

### **Dietary factors**

No consistent association has been observed between a variety of dietary factors and the risk of ovarian cancer.

A systematic review and meta-analysis that included 23 case-control studies and three cohort studies found no evidence of an association between alcohol use and epithelial ovarian cancer.[35]

A case-control study of the Healthy Eating Index (HEI), based on current U.S. Department of Agriculture dietary guidelines, found no association between the highest HEI score and ovarian cancer risk for any specific food group.[36] A systematic review of the role of diet in ovarian cancer included only prospective studies, with at least 200 reported cases in the publications.[37] Twenty-four publications from ten cohort studies were reviewed and no dietary factors were consistently associated with the risk of ovarian cancer.

### **Aspirin and nonsteroidal anti-inflammatory drugs**

A systematic review and meta-analysis of 21 observational studies found a decreased risk of invasive ovarian cancer associated with aspirin use (RR, 0.88; 95% CI, 0.79–0.98), but no statistically significant association with nonsteroidal anti-inflammatory drugs (NSAIDs).[38] A study published subsequent to that review examined NSAID use and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study. No association was observed between the development of ovarian cancer and regular aspirin use (RR, 1.06; 95% CI, 0.87–1.29) or NSAID use (RR, 0.93; 95% CI, 0.74–1.15).[39] A population-based case-control study [40] of 902 incident cases and 1,802 population controls observed a decreased risk of ovarian cancer associated with continual use (0.71; 95% CI, 0.53–0.97) or low-dose daily use (0.72; 95% CI, 0.53–0.97). In that study, selective cyclo-oxygenase-2 NSAIDs but not nonselective NSAIDs were associated with a decreased risk of ovarian cancer (OR, 0.60; 95% CI, 0.39–0.94). A cohort analysis of about 200,000 women in the Nurses' Health Studies, which used detailed data about the intensity and duration of aspirin use over time, showed a reduced HR for ovarian cancer of 0.77 (95% CI, 0.61–0.96) for low-dose aspirin use ( $\leq 100$  mg/d) but no reduction for standard-dose aspirin use (HR, 1.17; 95% CI, 0.92–1.49).[41]

### **Perineal talc exposure**

The weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer. Results from case-control and cohort studies are inconsistent. A meta-analysis of 16 studies observed an increased risk with the use of talc (RR, 1.33; 95% CI, 1.16–1.45); however, a dose response relationship was not found.[42] A pooled analysis from the Ovarian Cancer Association Consortium, composed of multiple case-control studies, included 8,525 cases and 9,859 controls, found a modest increased risk of epithelial ovarian cancer associated with genital powder use (OR, 1.24; 95% CI, 1.15–1.33), but the trend across



increasing lifetime number of applications was not statistically significant ( $P$  trend = .17).[43] A population-based case-control study of African American women in the United States found an association between genital powder use and risk of epithelial ovarian cancer (OR, 1.44; 95% CI, 1.11–1.86).[44] In this study of 584 cases and 745 controls, a dose-response relationship for *any* genital powder use was reported. Specifically, among *any* genital powder use, daily powder use was associated with increased adjusted OR of developing ovarian cancer (OR, 1.71; 95% CI, 1.26–2.33) compared with less than daily use (OR, 1.12; 95% CI, 0.80–1.58). A cohort study among nurses did not observe a risk of ovarian cancer associated with perineal talc use (RR, 1.09; 95% CI, 0.86–1.37) and there was no evidence of increased risk with increasing frequency of use.[45] Another prospective study, The Women’s Health Initiative, examined the association between perineal powder use and the development of ovarian cancer among 61,576 women without a history of cancer at enrollment and who provided exposure information. Among this group, 429 cases of ovarian cancer occurred. Powder use on genitals, sanitary napkins, and diaphragms was examined individually and as a combined exposure. Women were followed for a mean of 12.4 years. An association of ovarian cancer with ever-use was not found when analyzed either by individual method of exposure or by overall combined exposure. The observed risk (hazard ratio) for combined exposure to perineal powder was 1.06 (95% CI, 0.87–1.28) and there was no increased risk observed for increasing duration of use.[46]

## Areas of Uncertainty

### Ovarian hyperstimulation due to infertility treatment

Controversy persists concerning the association between ovarian hyperstimulation and ovarian cancer. Results of a systematic review and meta-analysis of nine cohort studies comprised 109,969 women who were exposed to ovarian hyperstimulation for infertility treatment (i.e., *in vitro* fertilization [IVF]), with 76 incident ovarian cancer cases observed, provided inconclusive evidence for an association.[47] An increased risk of ovarian cancer was observed when the comparison group was the general population (RR, 1.50; 95% CI, 1.17–1.92), but no statistically significant increased risk was observed when the reference group was unexposed infertile women (RR, 1.26; 95% CI, 0.62–2.55). A major limitation was that only one of the cohort studies included in the meta-analysis had a follow-up period longer than 10 years for those exposed to IVF.

A Cochrane systematic review that included 11 case-control studies and 14 cohort studies, for a total of 186,972 women, was also indeterminate for an association. Summary statistics were not calculated because of methodological and clinical heterogeneity. Among seven cohort studies that compared treated women with untreated subfertile women, no excess risk was noted in association with hyperstimulation medications. Two cohorts noted an increased risk of twofold to fivefold when treated women were compared with the general population. An increased risk of borderline ovarian tumors was noted in three case-control studies and two cohort studies. Overall, the authors concluded there was no convincing evidence that an increased risk of invasive ovarian tumors was associated with fertility drug treatments.[48]

After the Cochrane review, a follow-up study of an infertility cohort [49] was published. A retrospective cohort of 9,825 women enrolled between 1965 and 1988 was followed through 2010. Ovarian cancer occurred in 85 women. Overall, there was no association between ovarian cancer and clomiphene citrate (RR, 1.34; 95% CI, 0.86–2.07) or gonadotropins (RR, 1.00; 95% CI, 0.48–2.08). Among the subgroup of women who remained nulligravid after treatment, an increased risk of ovarian cancer was associated with clomiphene citrate (RR, 3.63; 95% CI, 1.36–9.72); no increased risk was observed among women who successfully conceived after being treated, compared with women who were not treated.

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## Changes to This Summary (03/01/2019)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

### Description of the Evidence

Updated [statistics](#) with estimated new cases and deaths for 2019 (cited American Cancer Society as reference 1).

Added [text](#) about a cohort analysis of about 200,000 women in the Nurses' Health Studies, which used detailed data about the intensity and duration of aspirin use over time, that showed a reduced hazard ratio for ovarian cancer of 0.77 for low-dose aspirin use but no reduction for standard-dose aspirin use (cited Barnard et al. as reference 41).

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**Updated:** March 1, 2019

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